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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/937,150	03/26/2002	Terrence R. Burke Jr.	401371	6328

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EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 04/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/937,150	BURKE JR. ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *1-9,24,27,30,31,35,86,91-93,107,113,118 and 119* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-49, 67, 68, 72, 73, 78, 85, 116, 117 and 120-123* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-9,24,27,30,31,35,39-49,67,68,72,73,78,85,86,91-93,107,113 and 116-123.

Pursuant to the directives of the response filed 2/26/04, claims 120-123 have been added. The following claims are now pending: 1-9, 24, 27, 30, 31, 35, 39-49, 67, 68, 72, 73, 78, 85, 86, 91-93, 107, 113, 116-123.

Applicants' election of Group 2 with traverse is acknowledged (claims 39-49, 67, 68, 72, 73, 78, 85, 116, 117). Claims 39-49, 67, 68, 72, 73, 78, 85, 116, 117 and 120-123 are examined in this Office action; claims 1-9, 24, 27, 30, 31, 35, 86, 91-93, 107, 113, 118, 119 are withdrawn from consideration.

✧

35 U.S.C §101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture or composition of matter or any new and useful improvement therof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claim 123 is rejected under 35 USC §101 because the claimed invention is not supported by a well-established utility.

Claim 123 recites that a disease can be "prevented". As it happens, there is no evidence that a disease can be "treated", but if, at some point in the future, applicants provide evidence that a disease can be successfully treated, this ground of rejection will be maintained because of the term "prevented". "Prevention" means that not a single test subject will develop any symptoms of a disease. For example, suppose that the

compound were administered to each of 1000 rats, and that a tumor were implanted into each of the rats. Suppose also, that in 999 of the rats, the tumor were completely eradicated within 10 seconds, but that one of the rats required fully six months to eradicate the tumor. Such a result would be considered "wildly successful" by any standard, yet the result would still constitute evidence of "failure" insofar as prevention is concerned. The reason is that one of the rats (out of 1000) failed to prevent the tumor from growing. The "bar" to overcome in demonstrating prevention is quite high, and not even a first step towards this goal has been undertaken. It is suggested that the term "preventing" be deleted from claim 123. (However, even if this is done, the §112, first paragraph rejection will still be maintained because of the term "treating").

Claim 123 is also rejected under 35 USC. §112 first paragraph. Specifically, since the claimed invention is not supported by a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

✧

Claim 39 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 or claim 11 of U.S. Patent No. 6,307,090. Although the conflicting claims are not identical, they are not patentably distinct from each other; there is overlap of the claimed genera.

The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. In re Vogel, 164 USPQ 619 (CCPA

1970). A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application . See 37 CFR 1.78(d)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 123 is rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 123 is drawn to a method of treating a disease. The disease is not specified, but one can infer that cancer is included. Unspecified inflammatory and autoimmune diseases might also be encompassed. However, treatment of these diseases (or any other diseases) is not enabled by the specification. As stated on page 27, line 31, the IC_{50} for MAP kinase inhibition for compound 126 is 12.5 micromolar. It is also asserted (page 28, line 10+) that compound 126 inhibits growth of MDA-MB 453 cells. Also asserted (page 28, line 12+) that compound 126 inhibits growth of MDA-MB 453/M1 breast cancer xenographs. Also asserted (page 44, line 16-17) is that compounds 11, 12 and 20a exhibited IC_{50} values in the range of 100 – 500 nM using the surface plasmon resonance SH2 domain binding assay

described in Yao (*J. Med. Chem.* **42** 25, 1999). On page 44, line 28+, it is asserted that addition of unidentified compounds to unidentified cells led the applicants to postulate that unidentified compounds of the invention have "cell killing activity". However, given that the cells were unidentified, the compounds were unidentified and the results have not been disclosed, it is entirely possible that this particular result is in error. For example, if inadequate controls are done, erroneous conclusions can result. If statistical analysis of results is required, erroneous conclusions can also result, especially if the biologist conducting the experiments is not adequately skilled in the art of statistical analysis. Accordingly, the assertion that unidentified compounds caused killing of unidentified cells is not found persuasive. On page 45, line 20+, it is asserted that compound 11 inhibited production of MAP kinase in MDA-453 cells that had been treated with heregulin. On page 45, line 30+, it is asserted that compound 126 inhibited colony formation of HBC-474 and MDA-453 cell lines. However, no data is reported, and again questions of control experiments and statistical analysis come to the fore.

Thus, what applicants have shown is that one or more compounds within the claimed genus are effective to inhibit MAP kinase, to inhibit binding of an SHC phosphopeptide to a protein containing a Grb2 SH2 domain, and that one or more compounds within the claimed genus can inhibit growth of certain cells. However, no evidence is presented that there exists even one disease which can be successfully treated in a patient by administering one of the claimed compounds.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988), the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. The following references discuss the matter of various attempts by oncologists to treat cancer: Viallet (*Lung Cancer* **15** (3) 367-73, 1996); Kemeny (*Seminars in Oncology* **21** (4 Suppl 7) 67-75, 1994); Newton (*Expert Opinion on Investigational Drugs* **9** (12) 2815-29, 2000); Giese (*Journal of Cancer Research and Clinical Oncology* **127** (4) 217-25, 2001); Garattini (*European Journal of Cancer* **37** Suppl 8 S128-47, 2001); Ragnhammar (*Acta Oncologica* **40** (2-3) 282-308, 2001). As is evident, attempts to treat cancer using agents which have exhibited *in vitro* activity leads to "unpredictable" results.

As mentioned on page 2, line 20+ (specification) and in Yao (*J. Med. Chem.* **42** 25, 1999), proteins containing the Grb2 SH2 domain are linked to signaling events involving RAS proteins. As it happens, attempting to treat cancer using farnesyl protein transferase inhibitors leads to "unpredictable" results:

- Moasser (*Breast Cancer Research and Treatment* **73** (2) 135-44, 2002) discloses (e.g., abstract) that FT inhibitor sensitivity does not correlate with the relative expression of Ras isoforms or the inhibition of Ras processing, growth factor signaling, expression of estrogen receptor or the overexpression of growth factor receptors. Also stated (last paragraph) is that Ras is not a molecular marker to

guide FT inhibition therapy. This reference does not support the proposition that attempts to treat cancer patients will necessarily result in failure. However, it does support the proposition that there may be many forms of cancer which will be resistant to the effects of FT inhibition.

- Jiang (*Molecular and Cellular Biology* **20** (1) 139-48, 2000) discloses that while AKT2- transformed NIH 3T3 cells are sensitive to FTI-277, but that *ras*-transformed NIH 3T3 cells are not. This supports the proposition that one cannot predict which cells will be sensitive to FT inhibitors.

- Prendergast (*Molecular and Cellular Biology* **14** (6) 4193-202, 1994) discloses that the FT inhibitor L-739,749 inhibited growth of ras-transformed fibroblasts. However, L-739,749 had no effect on the growth, morphology, or actin organization of v-*raf*-transformed cells. This supports the proposition that one cannot predict which cells will be sensitive to FT inhibitors.

- Njoroge (*J. Med. Chem.* 40 (26) 4290-301, 1997) discloses that the Ras farnesyl-protein transferase inhibitor SCH 44342 did not show appreciable *in vivo* antitumor activity. This supports the proposition that *in vitro* activity is not necessarily predictive of therapeutic efficacy.

- Lerner (*Oncogene* **15** (11) 1283-8, 1997) discloses that the Ftase inhibitor FTI-277 is highly effective at blocking oncogenic H-Ras but not K-Ras4B processing and signaling. The results obtained demonstrate that while FTI-277 inhibits N-Ras and H-Ras processing in the human tumor cell lines evaluated, inhibition of K-Ras processing requires both an FTase inhibitor and a GGTase I inhibitor.

- Whyte (*J Biol Chem* **272**, 14459, 1997) discloses that geranylgeranyl transferase-1 is structurally related to farnesyl transferase, and that geranylgeranyl transferase-1 may alternatively prenyl K-Ras, thereby bypassing the effect of FPTase inhibition.

- Sharma (*Annals of Oncology* **13** (7) 1067-71, 2002) discloses results of a phase II trial of SCH 66336, an FPTase inhibitor, in patients with metastatic colorectal cancer. No objective responses were observed. It is concluded that future development of this compound cannot be recommended as monotherapy in this disease.

Thus, attempts to treat cancer lead, in general, to "unpredictable" results, as do attempts to

treat cancer using Ftase inhibitors. Accordingly, it stands to reason that in attempting to treat cancer in humans using compounds which inhibit binding of an SHC phosphopeptide to a protein containing a Grb2 SH2 domain, "unpredictable" results will be obtained.

Accordingly, "undue experimentation" would be required to practice the invention of claim 123. It is suggested that the method claims be limited to a method of inhibiting proliferation of cells that exhibit amplified erbB-2 signalling, a method of inhibiting MAP kinase, and a method of inhibiting binding of phosphopeptides to proteins that contain an SH2 domain.

✧

Claims 39-49, 67, 68, 72, 73, 78, 85, 116, 117 and 120-123 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- In claim 39, it is recited, in reference to "W", that the alkyl and aryl portions of the substituents can be substituted with "keto". However, a "keto" group must bonded to two groups, not one. Accordingly, the claim is rendered indefinite as to what other substituent can be bonded to the keto group. Suppose, for example, that "W" is aryloxycarbonyl that is substituted with "keto". What is the range of options for structures that would correspond to this?

- In claim 39, the following is recited (last two lines):

  "contains a ...substitutent at a position *para-* to the alkylamido group".

  Here, the phrase "the alkylamido group" lacks antecedent basis.

- Claim 73 recites that the "heterocyclyl portion" of Z can be (among other possibilities) an indole group. However, this then raises a question about what is meant by the term "**aryl** heterocyclyl". Note that the term "heterocyclyl", without further qualification, could mean either an aromatic or non-aromatic heterocyclic group. Thus, for the case in which the "heterocyclyl portion" of Z is indole, what then would be an example of an "aryl heterocyclyl" group, such that the aryl heterocyclic group is different from the heterocyclic group?

- Claim 73 provides a structural formula for the "heterocyclyl portion" of Z. In this formula, there are dotted lines that define a circle. It is not clear what is intended by this. What organic chemists often intend by this denotation is that the presence of a double bond is optional, and if absent, there is a single bond. However, the situation in this case is complicated by the fact that reference is made to an "aryl heterocyclic" group. According to one interpretation, the fused ring structure containing "F" and "G" must be aromatic. If so, the two bridgehead carbon atoms must be sp2-hybridized, i.e., there must be a double bond between them. If there must be a double bond between them, then a double bond is not optional, and the "dotted line" denotation would then be misleading. On the other hand, if the fused ring structure containing "F" and "G" does not have to be aromatic, then for the cases in which the fused ring structure containing "F" and "G" is not aromatic, a third ring would have to be present in order to satisfy the requirement in the claims that an aryl heterocyclic group is present. Which interpretation is correct?

- Claim 117 (and claim 85) recites that the carrier is "pharmacologically acceptable". The term "pharmacology" pertains to the study of drugs. The term "pharmaceutical", on the other hand, pertains to formulation of drugs. Accordingly, it would seem more appropriate to recite that the carrier is *pharmaceutically acceptable*, than it is to recite that the carrier is "pharmacologically acceptable".

- Claim 122 recites that binding of an SH2 "domain" can be inhibited. However, an SH2 domain does not exist in and of itself. An SH2 domain exists as part of a larger molecule, usually a protein. A crude analogy here might be drawn between the SH2 domain of a protein, and one of the tires present on a car. Consider the following:

  A method of reducing the rate of movement of a tire comprising the step of

depressing a brake pedal.

In this case, one can envision what is likely intended, but the statement could be more clearly phrased. Similarly, claim 122 would be made more clear if it were conveyed that the SH2 domain is part of a protein.

- Claim 123 is drawn to various different embodiments, one of which is treatment of a disease. For this embodiment, the claim is indefinite as to which disease, or which type of disease may be intended.

- Claim 123 is drawn to a method of preventing or treating a disease, state or condition. However, uncertainty arises with regard to a "state or condition". As it happens, all living humans, however healthy, can be described as being in a state or condition (for better or worse). A healthy person, for example, is in a healthy condition. Why would one want to prevent or treat a healthy condition?

✧

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this action.

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 39, 40, 49, 72, 78, 85 are rejected under 35 U.S.C. §102(a) as being anticipated by

Al-Obeidi (USP 5,849,510).

Al-Obeidi discloses (col 22, line 15+) the following compound:

Ac-Tyr-Ile-Arg-NH-CH_2-pyridyl

This anticipates claim 39 when the substituent variables are as follows:

Y is Phe substituted with hydroxyl

W is alkylcarbonyl

n is 2

Z is heteroarylalkylamino

Thus, the claims are anticipated.

✧

Claims 39, 40, 49, 67, 78 are rejected under 35 U.S.C. §102(e) as being anticipated by Larsen (USP 6,410,585).

Larsen discloses (col 219) a compound designated "example 43". This anticipates claim 39 when the substituent variables are as follows:

W = carboxyalkylcarbonyl

Y = Phe substituted with carboxyalkoxy

n = zero

Z = 3-phenylpropylamino

Thus, the claims are anticipated.

✧

Claims 39, 40, 49, 67, 78 are rejected under 35 U.S.C. §102(e) as being anticipated by Horwell (USP 5,981,755).

Horwell discloses (col 21) the compound of example # 34. This anticipates claim 39 when the substituent variables are as follows:

W = benzyloxycarbonyl

Y = Phe substituted with hydroxyl

n = zero

Z = benzyl

Thus, the claims are anticipated.

✧

Claim 39 is rejected under 35 U.S.C. §102(e) as being anticipated by Burke (USP 6,307,090).

Burke discloses 5 compounds in claim 11 (col 67, line 48+). Each of these anticipates instant claim 39. The compounds in claim 11 are the first, third and fourth ones listed. With regard to the phosphonoalkyl and phosphonohaloalkyl groups, the proviso in the last two lines of claim 39 is noted. However, there is ambiguity as to what is intended by "the alkylamido group".

Thus, the claim is anticipated.

✧

Claim 39 is rejected under 35 U.S.C. §102(e) as being anticipated by Hiyoshi (USP 5,824,862).

Hiyoshi discloses (col 53) SEQ ID NO: 13 which has the following sequence:

G-Y-R-G-F-Y

This peptide anticipates the claims when applicants' substituent variables correspond as follows:

W = methylcarbonyl which is substituted with amino

Y = phenylalanine which is substituted with hydroxyl

AA^1 = arginine

AA^2 = glycine

AA^3 = phenylalanine

n = 3

Z = phenethylamino which is substituted with carboxyl and with hydroxyl.

The first point to be made here is that substituent variable "W" can represent any of several amino acids. For example, "W" can be any of the following: Gly, Val, Ile, Nle, Ala, Lys, Ser, Thr. This is because one can begin with an acyl group, and attach an amino group alpha- to the carbonyl, giving rise to glycine or an amino acid with an alkyl side chain. Further substitution with hydroxyl or amino is also permitted by the claims.

The second point concerns variable "Z", and substitutions which may be permitted there. It is true that, in claim 39, if one looks only at the last 5 lines of the claim, one would not necessarily conclude that the term "arylalkylamino" is such as to permit addition substitution on the alkyl portion of this group. However, earlier in the claim, the following is recited:

"wherein the alkyl portion of the substituents may be ... substituted with ... carboxyl"

It is not made clear what "the substituents" refers to. One interpretation is that this phrase can refer to any substituent within the claim. Thus, according to this interpretation, the "arylalkylamino" group can be substituted with carboxyl. This interpretation is reinforced, in a roundabout way, by claims 68 and 73, which convey that when the term "aryl" is used, this term includes substituted aryl. If the term "aryl" encompasses "substituted aryl", then it stands to reason that the term "alkyl" would include "substituted" alkyl.

Thus, the claims are anticipated.

✧

Claim 39 is rejected under 35 U.S.C. §102(e) as being anticipated by Harding (USP 6,022,696)

Harding discloses (col 59) SEQ ID No: 1, and (col 69) SEQ ID No: 14. These are, respectively, the following:

VYIHPF

KYIHPF

The first of these is encompassed by claim 39 when the substituent variables correspond

as follows:

W = alkylcarbonyl which is substituted with amino

Y = phenylalanine which is substituted with hydroxyl

AA^1 = Ile

AA^2 = His

AA^3 = Pro

n = 3

Z = phenethylamino which is substituted with carboxyl

As indicated above (the §102 over Hiyoshi), the claim can be interpreted to encompass the possibility of "Z" being substituted.

Thus, the claim is anticipated.

✧

Claim 39 is rejected under 35 U.S.C. §102(e) as being anticipated by Landry (USP 5,948,658).

Landry discloses (col 67) SEQ ID NO: 76 which has the following sequence:

D-Y-N-M-Y

This peptide anticipates the claims when applicants' substituent variables correspond as follows:

W = 2-methylpropionyl which is substituted with amino and with carboxyl

Y = phenylalanine which is substituted with hydroxyl

AA^1 = Asn

AA^2 = Met

n = 2

Z = phenethylamino which is substituted with carboxyl and with hydroxyl.

As indicated above (the §102 over Hiyoshi), the claim can be interpreted to encompass the possibility of "Z" being substituted.

Thus, the claim is anticipated.

✧

DAVID LUKTON
PATENT EXAMINER
GROUP 1653

[The patents cited by applicants on the IDS have been instead cited on a PTO-892. Examiners are required to list the class/subclass of each patent; citing the references on an 892 facilitates the realization of this objective, and provides greater legibility to the persons responsible for printing the final document].

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at 571-272-0951. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.